REMARKS

Claims 1-8, 10-15, 17, 20, 22, 25, 27, 30, and 33-40 are pending and rejected. Applicant notes that claims 9, 16, 18-19, 21, 23-24, 26, 28-29, and 31-32 were previously canceled without prejudice.

In this Amendment, claims 2-4, 7-8, 13-14, 27, 30, 33-36, and 39-40 are canceled without prejudice, and claims 1, 6, 11, 25, and 37 are amended.

Applicant and his undersigned representative thank the Examiner and SPE Page for the courtesy of a personal interview on December 16, 2005. During the interview, Applicant distinguished, over each reference, his claimed use of the macrolides rapamycin and/or ascomycin to specifically treat diabetic retinopathy, retinitis pigmentosa, or age related macular degeneration. None of the references, alone or in combination, disclose, suggest or motivate the use of rapamycin and/or ascomycin for these specific posterior segment ocular conditions.

Applicant appreciates acknowledgment that this Amendment will be considered and that agreement was reached. The previous amendment and following arguments are those agreed upon during the interview with the Examiner and SPE, now made of record.

CLAIM REJECTIONS UNDER 35 U.S.C. §102

Claims 1-4 are rejected under 35 U.S.C. §102(e) as anticipated by Robinson.

Claims 2-4 are canceled, rendering the rejection moot with respect to these claims. Claim 1 is amended to clarify use of the agent-containing matrix

at the front of the eye, to treat diabetic retinopathy, retinitis pigmentosa, or age related macular degeneration, disease in the back of the eye. The amendment adds the limitation of dependent claim 4, now canceled, and some limitations of dependent claim 3, now canceled.

As explained during the interview, Applicant's method treats these specific posterior segment diseases by implanting a rapamycin and/or ascomycin-containing matrix in the front of the eye (the sclera). This is not disclosed in Robinson, thus applicant believes this rejection is overcome and respectfully requests its withdrawal.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 5-8, 10-15, 17, 25, 27 and 33-36 are rejected under 35 U.S.C. §103(a) as obvious over Robinson in view of Kulkarni. Claims 7-8, 13-14, 27 and 33-36 are canceled, rendering the rejection moot with respect to these claims.

As previously analyzed, Robinson is distinguished over claims 5-6, 10-12, 17, and 25, each amended to clarify that rapamycin and/or ascomycin is administered to treat diabetic retinopathy, retinitis pigmentosa, or age related macular degeneration, which are posterior segment diseases. Robinson's disclosure of age related macular degeneration (column 9, lines 23-31), applied by the Examiner in her rejection, teaches implants with 2-methoxyestradiol or angiogenic compounds as therapeutic agents, not rapamycin and/or ascomycin. Thus, the primary Robinson reference fails.

Applicant disputes the Examiner rejection inasmuch as it is based on her finding that Robinson teaches topical delivery, ophthalmic drops, and topical ointment. In the very section the Examiner cites, Robinson teaches away from the use of these, in favor of Robinson's implant:

> Tight junctions between corneal epithelial cells limit the intraocular penetration of eye drops and ointments. Topical delivery to the eye surface via solutions or ointments can in certain cases achieve limited, variable penetration of the anterior chamber of the eye. However, therapeutic levels of the drug are not achieved and sustained in the middle or back portions of the eye. This is a major drawback, as the back (posterior) chamber of the eye is a frequent site of inflammation or otherwise the site of action where, ideally, ocular drug therapy should be targeted for many indications (column 2, lines 52-64, emphasis added).
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> ...
>
> As an approach for circumventing the barriers encountered by local topical delivery, local therapy route for the eye has involved direct intravitreal injection of a treatment drug through the sclera...However, the intravitreal injection delivery route tends to result in a short half life and rapid clearance, without sustained release capability being attained. Consequently, daily injections are frequently required to maintain therapeutic ocular drug levels, which is not practical for many patients (column 3, lines 24-33, emphasis added).

Therapeutic levels of agent that are non-achieved and non-sustained are not a method to treat an ocular condition, as applicant claims.

Moreover, rapamycin and ascomycin are very potent immunosuppressant drugs, so that the line between efficacy and toxicity (i.e., the therapeutic window) is very narrow. For such potent drugs administered locally to a small organ and in a confined space (i.e., "intraocular administration"),

applicant's claimed concentrations are more than "optimization" by "routine experimentation". Rapamycin and ascomycin can be toxic to the retina. Thus, the therapeutic concentration must be below the toxic concentration. Moreover, many ocular conditions are chronic and thus require long-term treatment, even over many years or decades. This further confounds intraocular administration, where toxic concentrations can accumulate. However, applicant's method provides for local administration of rapamycin and/or ascomycin in non-toxic concentrations (less than 200 μg/ml by intraocular injection; between 3-5 mg by ocular implantation).

Thus, while Robinson at best could be an invitation to experiment using rapamycin and/or ascomycin, there is no reasonable expectation of success with any route other than Robinson's matrix, based on Robinson's own disclosure. Thus, applicant disagrees with the Examiner that

> While Robinson et al. do not explicitly teach that their preferred method of administration is topical administration and/or intraocular injection, this would not deter the teaching to one of ordinary skill in the art that the prior art demonstrates how one of ordinary skill would use topical administration forms and/or intraocular injections (Office Action, page 6).

Because the primary Robinson reference fails, Kulkarni combined with Robinson does not render applicant's claims obvious. The Examiner states one skilled in the art would modify Robinson to include the topical and intraocular injectable administration forms of Kulkarni. Applicant has pointed out why one skilled in the art would not do this, based on Robinson's own disclosure of problems with topical and injectable administration routes, and why one skilled in

the art would not have a reasonable expectation of success to treat a posterior segment disease by an anterior segment route of administration. Thus, Applicant believes this rejection is overcome and respectfully requests its withdrawal.

Claims 20, 22, 30, and 37-40 are rejected under 35 U.S.C. §103(a) as obvious over Robinson in view of Ueno. Applicant respectfully disagrees. Claims 30 and 39-40 are canceled, rendering the rejection moot with respect to these claims.

Applicant reiterates his above distinctions over Robinson. Because the primary reference fails, Ueno combined with Robinson does not render applicant's claims obvious. Further, the rejection is improper because Ueno discloses ocular ointments, installations, applications, etc. which are all topical formulations. Ueno is not properly combined with Robinson, because of Robinson's explicit teaching away from topical formulations.

CONCLUSION

Applicant believes the application is in condition for allowance and respectfully requests a Notice of Allowance. Applicant submits a Request for Continued Examination with this Amendment. The Examiner has authorization to charge the fee of $395.00 to Deposit Account No. 23-3000. Applicant does not believe there is any other fee due with this submission. Should any fees or surcharges be deemed necessary, the Examiner has authorization to charge fees or credit any overpayment to Deposit Account No. 23-3000.

The Examiner is invited to telephone applicant's undersigned representative with any questions or issues.

Respectfully submitted,
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